REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. In the present amendment, claims 10, 18 and 46 have been amended, claim 12 has been cancelled, and claims 47-55 have been added. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Thus, claims 10, 11, 13, 14, 16-20, and 46-55 are pending in the application.

Claims Rejections - 35 USC § 112

Claims 10-12 and 15-19 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner questions whether the functional language "operable as an optical tweezers" describing the laser light source requires a second optical tweezers. Applicants respectfully traverse this rejection.

As illustrated in Figs. 2A and 2B and described in paragraphs [0057]-[0064] of the specification, optical tweezers "are tightly focused beams of laser light." The claim only recites one optical tweezers. The optical tweezers comprises the laser light source and the series of lenses which focus the light. Applicants believe the claim is clear and definite and respectfully requests withdrawal of the rejection. Applicants respectfully traverse this rejection.

Claims Rejections - 35 USC § 102

Claims 10 and 46 were rejected under 35 U.S.C. 102(a, b) as being anticipated by Dorre or Namba (JP-2003-189852). Applicants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegall Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Independent claim 10 has been amended to include the features of canceled claim 12. Specifically, independent claim 10 has been amended to include "a light source and a Raman detector to detect a single molecule by a surface enhanced Raman spectroscopy, the first channel being in optical communication with the light source and the Raman detector." Neither Dorre nor Namba teach "a Raman detector to detect a single molecule by a surface enhanced Raman spectroscopy emission." Both Dorre and Namba teach the use of fluorescence. Thus, neither Dorre nor Namba anticipate claim 10 or any of the claims that depend on claim 10.

Claim 46 has been amended to include the feature "wherein the first channel is separate and distinct from the restriction barrier such that there is a gap between a wall of the channel and the restriction barrier." Support for this feature can be found in Figs. 1, 2A and 2B and paragraphs [0057]-[0058] of the specification. Even if the angled walls of the microchannels of Dorre (Figure 1) and Namba (Figure 4) are restriction barriers, and Applicant does not concede this is true, the microchannels of Dorre and Namba do not include "a gap between a wall of the channel and the restriction barrier." Further, as described in paragraph [0058] of the specification, "[t]he optical tweezers 210 then capture a single particle 150 with an attached nucleic acid molecule 160 downstream from the restriction barrier 140 and downstream of a junction of the first channel 100 and the second channel 220 and/or third channel 230, transport the particle 150 upstream of a restriction barrier 140, and release the particle. The particle 150 is then moved by the flow of the first channel 100 into the restriction barrier 140 inside which it is restrained." The structural

configuration of both Dorre and Namba is not only different, it is incapable of performing the described function. Thus, neither Dorre nor Namba anticipate claim 46 or any of the claims that depend on claim 46.

Claims Rejections - 35 USC § 103

Claims 12-14, 16-17 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Dorre or Namba as applied to claims 10 or 46 above, and further in view of Ishikawa or Kneipp (US 2002/0150938, Physical Review E 1998, or Indian Journal of Physics, B abstract in chemical abstracts, hereinafter referred to as Kneipp 2002, Kneipp '98 and Kneipp '03, respectively).

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified or render it inoperable, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Independent claim 13 includes the feature of "a *Raman detector* configured to detect a *single* molecule by a surface enhanced Raman spectroscopy." Neither of the base references, Dorre or Namba, teaches a Raman detector. Indeed, both references teach the use of fluorescence for detection. As discussed in more detail in the attached declaration of Dr. Tae-Woong Koo, the combination of Dorre or Namba with Ishikawa, Kneipp 2002, Kneipp '98 or Kneipp '03 would render the apparatuses of Dorre and Namba inoperable. Specifically, as discussed in the declaration Dr. Koo, the fluorescent apparatuses of Dorre and Namba require detection time of 0.1 seconds or less:

> (a) The Dorre publication describes an apparatus and the method for sequencing a single nucleic acid molecule with ***fluorescent*** analogs substitute for the normal basis. Dorre provides that

> The fact that single fluorescent molecules can be identified within milliseconds [10] has opened up the horizon for an entirely different approach for sequencing RNA or DNA... This molecule may be degraded sequentially with the help of exonuclease. ***Provided that the released monomers can be detected according to the order of liberation from the polymer substrate,*** *the sequence analysis can be performed* ***at the rate of the enzymatic degradation (≈1-10 bases s-1).*** [Emphasis added.]

Dorre's description emphasizes the emergence of detection techniques that can detect single fluorescent molecules within milliseconds range as a key element to the single DNA/RNA sequencing. ***At the minimum, the Dorre apparatus requires that the detection speed to be equal to or faster than the release speed of the monomers (i.e. nucleotides).*** Otherwise, multiple nucleotides will be detected during a slow measurement and the sequence information is lost. As described by Dorre and as confirmed by Oijen et al. ("Exonuclease Reveal Base Dependence and Dynamic Disorder," Science, 301:1235-1238 (2003)), the speed of exonuclease is not constant. If Dorre's experimental setup releases single nucleotides at the rate between 1 and 10 bases per second, Dorre's experimental setup requires the detection of nucleotides every 0.1 second, which is the inverse of 10 bases per second, or less. For example, when the exonuclease operates to release 10 bases per second, a detector that takes one second will detect the presence of the ten bases without their relative sequence information. As a result, the sequence information will be lost. Therefore, a detection methodology that takes 1 (one) second for each measurement will not be able to detect individual nucleotides coming at the speed between 1 and 10 bases per second, and will not be able to provide the sequence information. (Koo at 2-3).

Kneipp, however, teaches a detection time of 1 second which is incompatible with Dorre:

> The Kneipp experiment shows in Figure 15 that the detection of single adenine molecule takes one second. Paragraph [0040] of Kneipp '938 provides "FIG. 15 shows typical SERS Stokes spectra representing approximately "1" (top), "0" (middle), or "2" (bottom) adenine molecules in the probed volume where **the collection time is 1 s** and at the excitation radiation is 80 mW near infrared radiation." (emphasis added)." Because the Kneipp method takes one second to detect a single adenine molecule, the Kneipp method cannot be combined with Dorre for the reason discussed above (i.e., the combination will lose the sequence information due to the slow detection). Thus, ***by combining Kneipp's Raman detection apparatus with Dorre's apparatus/method one would have***

> ***simply destroyed Dorre's apparatus/method*** as the combined apparatus/method would ***not*** work for Dorre's intended purpose of obtaining sequence information of RNA or DNA by sequentially degrading the RNA or DNA molecule with the help of an exonuclease. (Koo at 3-4).

Additionally, as discussed in the attached declaration, the detection time of Kneipp was selected to be one second to obtain an acceptable signal to noise ratio for the detection of a single adenine molecule, which is a base not a nucleotide. (Koo at 4). Even with a one second detection time, Kneipp's equipment would not be able to detect a single nucleotide released from a DNA molecule due to exonuclease activity. (*Id.*) This is because the intensity of nucleotides is much weaker than the intensity of bases. (*Id.*) Indeed,

> Because Kneipp's apparatus and method takes at least one second to detect a single adenine molecule and longer to detect a single dAMP molecule, and because the signal-to-noise ratio of Kneipp's apparatus and method in the detection of a single adenine molecule or a single dAMP would be poor if the detection time was within 0.1 second, a person trying to combine Dorre and Kneipp to sequence DNA using a Raman detection would face two unworkable options: increasing the collection time to obtain adequate signal-to-noise ratio in detection of single dAMP molecules at the expense of losing the sequence information, or reducing the detection time with the intent of collecting the sequence information at the expense of significantly degrading the signal-to-noise ratio to an unusable level. Neither of them would have been acceptable for a single molecule sequencer. (Koo at 5)

Further, as discussed in that attached declaration, the apparatus of Namba is similar to Dorre and operates in the same way. (Koo at 5). It therefore also requires a detection time of 0.1 seconds or less. Because detection time of Kneipp is one second and both Dorre and Nambe require a detection time of 0.1 seconds or less, Kneipp cannot be combined with Dorre or Namba.

Regarding Ishikawa, please note that it relates to "Single-Molecule Imaging and Spectroscopy Using Fluorescence and Surface-Enhanced Raman Scattering" as stated in the title of

Ishikawa. Combining the fluorescence measurement of Ishikawa with Dorre or Namba (which also teach fluorescent measurements) would not lead persons of ordinary skill in this art to the apparatus of claim 13 which recites "a Raman detector configured to detect a single molecule by a surface enhanced Raman spectroscopy." Thus, the appropriate question is whether the combination of the surface enhanced Raman scattering measurements of Ishikawa with Dorre or Namba would have lead to persons of ordinary skill in the art to the apparatus of claim 10. Applicants respectfully submit that the answer is "no" for the following reasons.

Paragraph 5 of the Koo declaration explains:

> The Ishikawa method is similar to the Kneipp method to the extent that it provides a Raman detector that can detect a single adenine molecule, wherein the "[d]ata accumulation time was 1 s" as explain the description of Figure 7 of Ishikawa. Therefore, the Ishikawa-Dorre or Ishikawa-Namba apparatus/method will not be operable for the reasons discussed above.

Because the Raman detection method of Ishikawa, like that of Kneipp, requires data accumulation time of 1 second in order to detect an adenine molecule, the Raman detector of Ishikawa is incapable of detecting single molecules with a data accumulation time of 0.1 second or less as required by the apparatus of Dorre or Namba. Thus, the combination of the disclosed Raman detection method of Ishikawa with the single molecule DNA sequencing apparatus of Dorre or Namba simply would ***not*** work because, as explained above, the apparatus of both Dorre and Namba require that the data accumulation time for detecting each nucleotide should be 0.1 second or less. For at least these reasons, no combination of Dorre or Namba with Ishikawa, Kneipp 2002, Kneipp '98 or Kneipp '03 render independent claim 13 or any of the claims that depend on independent claim 13 obvious.

Unexpected Results

Even assuming that the cited prior art establishes a *prima facie* case of obviousness, which Applicants respectfully deny, the Examiner is requested to consider the *unexpected results* of the claimed invention. The unexpected results are at least shown in paragraph (6) of Dr. Tae-woong Koo's declaration wherein he explains that he was able to detect single nucleotide molecules using Raman spectroscopy within 0.1 second. This detection time is a ten-fold improvement over the data accumulation time of Kneipp or Ishikawa as explained in Dr. Tae-woong Koo's declaration.

New Claims

New claims 47-50 depend on independent claim 10. New claims 51-54 depend on independent claim 46. New claim 55 depends on independent claim 13. Thus, these claims are allowable for at least the reason above.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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